Respiratory Medicine (2014) 108, 722–728

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD

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Received 18 July 2013; accepted 3 March 2014
Available online 20 March 2014

KEYWORDS
COPD;
Hypercapnia;
Non-invasive positive pressure ventilation;
BIPAP;
Respiratory failure;
Non-invasive ventilation

Summary
Rationale: Patients with COPD and hypercapnic respiratory failure have a worse prognosis and experience a faster deterioration in their pulmonary function. The benefit of home NPPV following an acute exacerbation of COPD with hypercapnic respiratory failure is not well understood.
Objectives: To evaluate the effect of home NPPV use in patients following a hospitalization for AECOPD with acute hypercapnic respiratory failure on event-free survival after an index admission.
Methods: We conducted a retrospective, single-center, chart review on patients hospitalized in 2011 with a diagnosis of AECOPD, hypercapnia, and used NPPV during hospitalization. 166 patients were included and were divided into two groups: patients who used NPPV post discharge and patients who did not.
Results: Patients in the NPPV post discharge group demonstrated superior event-free survival compared to the no-NPPV post discharge group ($\psi^2 = 23.8$, $p < 0.0001$). The NPPV post discharge group had a statistically significant reduction in hospital readmissions (40% versus 75%, $p < 0.0001$) through 180 days from the index admission.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AHRF, acute hypercapnic respiratory failure; COPD, chronic obstructive pulmonary disease; EPAP, expiratory positive airway pressure; FVC, forced vital capacity; HRQoL, health-related quality of life; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; NPPV, non-invasive positive pressure ventilation.

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http://dx.doi.org/10.1016/j.rmed.2014.03.006

Conclusions: Patients who used NPPV following an admission for AECOPD with hypercapnic respiratory failure had lower readmission rates and improved event-free survival after 180 days from an index admission compared to patients who did not use NPPV post discharge.

Introduction

Chronic obstructive pulmonary disease (COPD) continues to be a leading cause of morbidity and death in the United States and worldwide [1—3]. Hypercapnic respiratory failure is a phenomenon that may occur during acute exacerbations of COPD (AECOPD) and chronically as the disease progresses [4]. Patients with COPD and hypercapnic respiratory failure have a worse prognosis, are more likely to be admitted to the hospital, and experience a faster deterioration in their pulmonary and non-pulmonary function [5,6,25]. Once hypercapnia develops, the two-year mortality rate for COPD patients increases to 30—40% [7].

Non-invasive positive pressure ventilation (NPPV) has been shown to be an effective treatment for acute hypercapnic respiratory failure (AHRF) during COPD hospitalization. The use of NPPV in this setting reduces mortality, decreases the need for endotracheal intubation, and reduces the duration of hospitalization [8—10,17,23,26]. Patients with altered levels of consciousness that is mild may also tolerate NPPV during hospitalization for AECOPD [24].

The benefits, if any, from using home NPPV for chronic hypercapnic respiratory failure is less clear. Improvements in dyspnea scores and health-related quality of life (HRQoL) measures have been established in stable severe COPD with chronic hypercapnic respiratory failure [11—13,17,20]. In stable severe COPD the long-term effects of NPPV on spirometry and arterial blood gas measurements are conflicting [11—14,20]. Additionally, a mortality benefit or a reduction in COPD exacerbations from the use of NPPV in these patients has not been consistently demonstrated [15—17,19].

The majority of studies that have assessed home NPPV have evaluated severely obstructed but stable COPD patients with minimal hypercapnia. The benefits of home NPPV during the period of clinical instability that immediately follows AECOPD hospitalization and acute hypercapnic respiratory failure have not been well studied. We hypothesized that patients who used home NPPV immediately following an AECOPD admission with acute hypercapnic respiratory failure would have improved event-free survival compared to patients who did not use NPPV post discharge.

Methods

Patients

We conducted a retrospective, single-center, chart review in patients admitted for AECOPD with hypercapnic respiratory failure who received bilevel NPPV during hospitalization. A total of 1429 consecutive admissions with a primary or secondary discharge diagnosis of AECOPD from January 2011 to December 2011 were reviewed. All admissions were from a single academic university hospital in Philadelphia, Pennsylvania. Inclusion criteria were a primary or secondary discharge diagnosis of AECOPD (ICD-9 code 491.21), hypercapnic respiratory failure during hospitalization (defined as $PaCO_2 > 45$ mmHg on arterial blood gas), and the use of bilevel NPPV during hospitalization. Exclusion criteria were patients discharged to hospice, patients who did not receive an arterial blood gas during their hospital stay (no documented hypercapnia), and patients who did not receive NPPV during hospitalization. IRB approval was obtained from the Office for Human Subjects Protections Institutional Review Board of Temple University (approval number: 20135).

Study design

Patients who qualified for the study were divided into two groups: patients who used NPPV post discharge, and patients who did not use NPPV following discharge. The latter group consisted of patients who were not prescribed NPPV at the time of discharge and patients discharged with NPPV who were determined to be noncompliant. Compliance with bilevel NPPV was determined through review of both the outpatient electronic medical record and documentation in subsequent readmissions. Data related to home ventilator meter hours was not available and did not contribute to the determination of compliance. In the case of technical problems with the home ventilator, patients were expected to contact their pulmonologist and durable medical equipment provider to troubleshoot and resolve such issues.

Data was collected pertaining to the index admission that included patient comorbidities, endotracheal intubation, admission to the intensive care unit, length of hospital stay, demographics, arterial blood gas values on admission and at discharge, discharge medications, and IPAP and EPAP settings for bilevel NPPV at discharge. For individual patients who had multiple admissions that met the eligibility criteria for our study, the first admission chronologically was considered the index admission. Pulmonary function test and echocardiogram results were historical data obtained from the electronic medical record.

Study outcomes

The primary outcome for our study was event-free survival. This was defined as time after the index admission without re-hospitalization or death. Secondary outcomes were readmission rates, all-cause mortality rates, readmission rates to the intensive care unit (ICU), and readmissions requiring endotracheal intubation. Data for the secondary

outcomes were collected at 30, 90, and 180 days after the index admission. Readmission data was obtained through an electronic medical record that documented readmissions at our institution. Mortality data was obtained through documented deaths during readmissions and from the social security death index.

Analysis and statistics

The study results are expressed as a percentage or mean ± standard deviation. Statistical analysis was performed using Fisher's exact and Student's *t* test. Kaplan Meier analysis was performed for event-free survival. Cox regression analysis was performed to assess the association of NPPV use and event-free survival with other significant variables. The two study groups were subsequently matched using propensity scores derived from the variables age, BMI, FEV_1, OSA/OHS, Home O_2, $PaCO_2$ at discharge, and admission date. Characteristics that differed after propensity score matching were further adjusted for.

Results

Baseline characteristics and patient population

Of the 1429 admissions for AECOPD that were reviewed, 166 patients were included in the study (Fig. 1). The primary reason for study exclusion was that they had not received bilevel NPPV during hospitalization (1251 patients). In addition, seven patients were excluded who were discharged to hospice, while five patients were excluded for not having documented hypercapnia. Of the 166 patients who met inclusion criteria, 78 of these patients constituted the NPPV post discharge group while 88 patients comprised the no-NPPV post discharge group (Fig. 1).

The reason for not being prescribed NPPV at the time of discharge varied within the no-NPPV post discharge group. Physician discretion was the most common reason for not being prescribed home NPPV and occurred in thirty-six patients. Twelve patients could not obtain insurance approval for home NPPV, while sixteen patients declined home NPPV during discharge planning of the index admission.

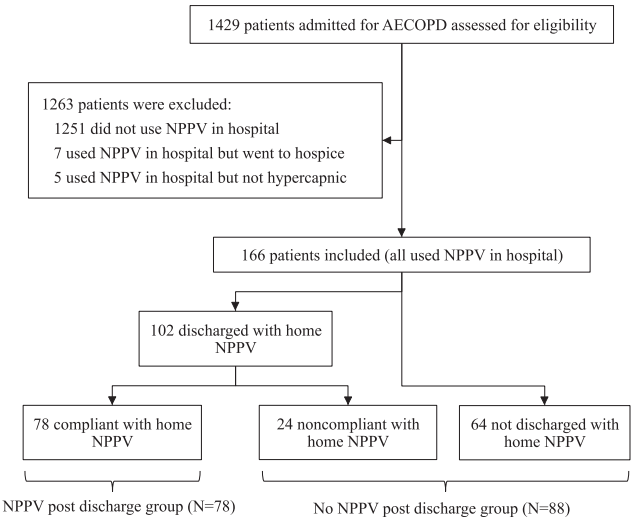

Figure 1 Flow diagram representing the study patient population.

There were several differences in the baseline characteristics of the two study groups (Table 1). The mean age of the NPPV post discharge group was 3.3 years younger than the no-NPPV post discharge group (61.6 versus 64.9 years), which was statistically significant ($p = 0.04$). Overall, women comprised 63% of the study population with more women than men in both study groups. The NPPV post discharge group had a greater proportion of patients with a history of obstructive sleep apnea or obesity hypoventilation syndrome than the no-NPPV post discharge group (47.4% versus 26.1%), which was statistically significant ($p = 0.006$). Race distribution was similar in both groups, with African American patients comprising 51% of the study population.

Historical data for pulmonary function tests were available for 104 of the 166 study patients. The percent predicted forced vital capacity (FVC) was lower in the NPPV post discharge group (59% versus 68.7%, $p = 0.01$). No other spirometry measurements were significantly different between the two groups. The majority of patients (157 of 166) had an echocardiogram in the electronic medical record. There was a similar prevalence of diastolic and systolic heart failure in the respective groups. Previous cardiac catheterization data was available for 59 of the 166 patients. This revealed a similar prevalence of coronary artery disease and pulmonary hypertension in the two study groups.

A higher proportion of index admissions involved ICU stays in the no-NPPV post discharge group compared to the NPPV post discharge group (71.6% versus 47.4%, $p = 0.002$). Discharge $PaCO_2$ was also significantly lower in the no-NPPV post discharge group than in the NPPV post discharge group (55.2 mmHg versus 61.2 mmHg, $p < 0.001$). In the NPPV post discharge group the mean IPAP setting at discharge from the reference admission was 22.1 ± 6.2 cm H_2O while the mean EPAP setting was 5.9 ± 1.8 cm H_2O.

Mortality and readmission rates

The NPPV post discharge group had a statistically significant reduction in hospital readmissions at 30, 90, and 180 days from the index admission (Table 2). At 180 days, 75% of patients in the no-NPPV post discharge group had at least one readmission, while only 39.7% of the patients in the NPPV post discharge group did ($p = 0.002$). There was a trend towards reduced mortality in the NPPV post discharge group in comparison to the no-NPPV post discharge group (10% mortality versus 19% mortality at 180 days, $p = 0.13$), but these values did not reach statistical significance.

ICU readmissions and intubation rates

The NPPV post discharge group had a reduction in the rate of readmissions requiring a stay in the intensive care unit. This reduction reached statistical significance at 30, 90, and 180 days of follow-up from the index admission (Table 2). The NPPV post discharge group also had a lower rate of

Table 1 Baseline characteristics & index admission data.

Baseline characteristic	Used NPPV post discharge ($N = 78$)	No-NPPV post discharge ($N = 88$)	P value
Age (years)	61.6 ± 10.2	64.9 ± 10.8	0.04
Body mass index (kg/m^2)	33.7 ± 12.0	30.6 ± 13.0	0.11
Current smoker — no. (%)	15 (19.2%)	24 (27.3%)	0.27
Race — no. (%)			
Caucasian	30 (38.5%)	27 (30.7%)	0.33
Black	40 (51.3%)	45 (51.2%)	1.00
Hispanic	8 (10.2%)	15 (17.0%)	0.26
Other	0 (0%)	1 (1.1%)	1.00
Male sex — no. (%)	33 (42.3%)	29 (33.0%)	0.26
Past medical history — no. (%)			
OSA/OHS	37 (47.4%)	23 (26.1%)	0.006
Pulmonary HTN	20 (25.6%)	21 (23.9%)	0.86
CHF (EF < 40%)	7 (9.0%)	11 (12.5%)	0.62
Diastolic dysfunction	37 (47.4%)	35 (49.8%)	0.43
CAD	19 (24.4%)	16 (18.2%)	0.35
CVA	3 (3.9%)	7 (8.0%)	0.34
DM	37 (47.4%)	30 (34.1%)	0.08
HTN	64 (82.1%)	73 (83.0%)	1.00
Lung cancer (active)	2 (2.6%)	5 (5.7%)	0.45
Other cancer (active)	1 (1.3%)	4 (4.6%)	0.37
Spirometry			
FEV_1 (% predicted)	34.5 ± 16.3 ($n = 57$)	40 ± 16.3 ($n = 47$)	0.09
FVC (% predicted)	59 ± 19.8 ($n = 57$)	68.7 ± 18.9 ($n = 47$)	0.01
FEV_1/FVC ratio	0.47 ± 0.2 ($n = 57$)	0.47 ± 0.2 ($n = 47$)	0.90
RV (% predicted)	154.6 ± 65.7 ($n = 43$)	152.6 ± 65.8 ($n = 34$)	0.89
TLC (% predicted)	92.9 ± 28.4 ($n = 43$)	98.9 ± 27.9 ($n = 34$)	0.36
RV/TLC ratio	58.2 ± 11.8 ($n = 43$)	56.7 ± 13.4 ($n = 34$)	0.60
Index admission			
ICU — no. (%)	37 (47.4%)	63 (71.6%)	0.002
Intubated — no. (%)	14 (18.0%)	21 (23.9%)	0.45
Length of stay (days)	9.9 ± 8.5	9.5 ± 7.5	0.77
pH on admission	7.30 ± 0.08	7.27 ± 0.1	0.03
$PaCO_2$ on admission (mmHg)	74.6 ± 17.8	76.8 ± 23.4	0.49
pH at discharge	7.40 ± 0.04	7.42 ± 0.05	0.03
$PaCO_2$ at discharge (mmHg)	61.2 ± 11.2	55.2 ± 11.4	<0.001
Discharge medications			
Home O_2 — no. (%)	64 (82.1%)	61 (69.3%)	0.07
Prednisone — no. (%)	61 (78.2%)	71 (80.7%)	0.70
Antibiotic — no. (%)	25 (32.1%)	25 (28.4%)	0.62
LABA — no. (%)	70 (89.7%)	76 (86.4%)	0.63
SABA — no. (%)	76 (97.4%)	88 (100%)	0.22
ICS — no. (%)	69 (88.5%)	76 (86.4%)	0.82

Data are presented as mean ± SD unless otherwise specified.
OSA, obstructive sleep apnea; OHS, obesity hypoventilation syndrome; HTN, hypertension; CHF, congestive heart failure; CAD, coronary artery disease; CVA, cerebrovascular accident; DM, diabetes mellitus; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; ICU, intensive care unit; $PaCO_2$, arterial carbon dioxide tension; LABA, long acting beta agonist; SABA, short acting beta agonist; ICS, inhaled corticosteroid.

readmissions requiring endotracheal intubation, which reached statistical significance at 180 days of follow-up.

Event-free survival

We constructed a Kaplan—Meier survival curve for event-free survival as time measured from the index admission. Patients in the NPPV post discharge group demonstrated superior event-free survival as compared to the no-NPPV post discharge group ($\chi^2 = 23.8$, $p < 0.0001$) (Fig. 2).

Cox regression analysis and propensity scores for event-free survival

A multivariate analysis was performed using a Cox regression model to identify baseline characteristics associated

Table 2 Results for secondary endpoints comparing NPPV post discharge versus no-NPPV post discharge.

	Used NPPV post discharge ($N = 78$)	No-NPPV post discharge ($N = 88$)	*P* value
Number of patients with readmission — no (%)			
At 30 days	12 (15%)	35 (40%)	<0.001
At 90 days	20 (26%)	53 (60%)	<0.0001
At 180 days	31 (40%)	66 (75%)	<0.0001
Number of patients with readmission to ICU — no (%)			
At 30 days	2 (3%)	12 (14%)	0.01
At 90 days	5 (6%)	20 (23%)	0.004
At 180 days	6 (8%)	28 (32%)	0.0001
Number of patients intubated at readmission — no (%)			
At 30 days	1 (1%)	7 (8%)	0.07
At 90 days	4 (5%)	11 (13%)	0.11
At 180 days	5 (6%)	16 (18%)	0.03
Mortality — no (%)			
At 30 days	3 (4%)	6 (7%)	0.5
At 90 days	6 (8%)	11 (13%)	0.44
At 180 days	8 (10%)	17 (19%)	0.13

NPPV, non-invasive positive pressure ventilation; ICU, intensive care unit.

with reduced event-free survival (Table 3). No-NPPV at discharge, home O_2 use, LABA use, and pulmonary HTN were variables associated with reduced event-free survival. The two study groups were subsequently matched with the use of propensity scores. Propensity scores for group matching were calculated using the variables of age, BMI, FEV_1, OSA/OHS, $PaCO_2$ at discharge, home O_2, and admission date. The matching process resulted in 77 patients from the NPPV post discharge group being statistically matched with 77 patients from the no-NPPV post discharge group. After matching with propensity scores the characteristics OSA/OHS and $PaCO_2$ at discharge still differed between groups. These two variables were further adjusted for between the matched groups (Table 3). Subjects who did not use NPPV post discharge had inferior event-free survival through 180 days after statistical matching compared to patients who used NPPV post discharge (HR 3.29, 95% CI 2.05—5.27, $p < 0.0001$) (Table 3).

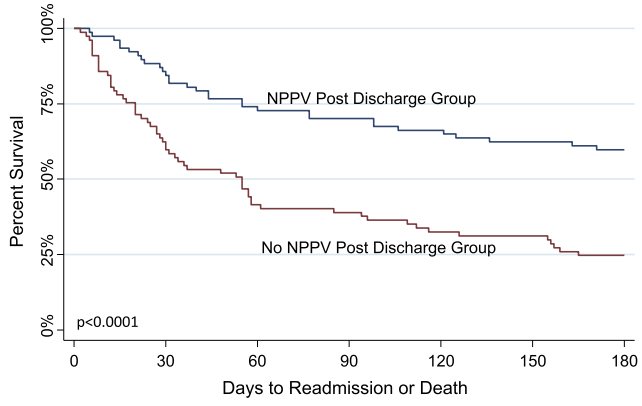

Figure 2 Kaplan Meier curve of event-free survival comparing patients who used NPPV post discharge versus patients who did not use NPPV post discharge.

Discussion

Our retrospective study demonstrated that patients who used home NPPV following hospitalization for AECOPD with acute hypercapnic respiratory failure had improved event-free survival and reduced readmission rates through six months compared to patients who did not use NPPV post discharge. Patients who used NPPV post discharge also had lower readmission rates at six months, and a reduction in readmissions requiring admission to the intensive care unit.

In a randomized controlled trial, Cheung and others demonstrated that continued home NPPV use following an AECOPD with acute hypercapnic respiratory failure (AHRF) reduced the recurrence of severe AECOPD with AHRF (requiring intermittent NPPV, intubation, or resulting in death) at one year compared to a control group using home CPAP [27]. While our study looked at different primary and secondary endpoints, our findings of reduced need for endotracheal intubations and reduction in readmissions to the intensive care unit through 180 days indirectly corroborates Cheung and others findings that continued home NPPV reduces recurrent severe AECOPD. Also in agreement with our study, Cheung and colleagues did not demonstrate a reduction in death from the continued use of NPPV.

One limitation of our study is that readmission data was only collected from our home institution's health care system. Consequently, this inevitably resulted in a lower reported readmission rate for both study groups. While unlikely, it cannot be excluded that this may have skewed the readmission rates in favor of the NPPV post discharge group. Another limitation is the possibility of noncompliance as a confounding factor in the no-NPPV post discharge group. Twenty-four of the eighty-eight patients (27.3%) in the no-NPPV post discharge group consisted of patients who were documented to be noncompliant with home NPPV. The possibility that these patients were also noncompliant with other home medications for COPD cannot be excluded and this could have contributed to their poorer outcomes.

Table 3 Association of NPPV and event-free survival with propensity score matching and Cox regression analysis.[a]

Variable	Univariate		Multivariate[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
NPPV (no versus yes)	3.11 (1.99—4.87)	<0.0001	3.29 (2.05—5.27)	<0.0001
Home O_2	1.93 (1.10—3.39)	0.02	1.94 (1.10—3.41)	0.02
LABA	2.57 (1.16—5.66)	0.02	2.62 (1.16—5.92)	0.02
Pulmonary HTN	1.74 (1.09—2.76)	0.02	1.77 (1.11—2.84)	0.02

CI, Confidence interval; HR, Hazard ratio; NPPV, Non-invasive positive pressure ventilation; LABA, long acting beta agonist; HTN, hypertension.

[a] Propensity scores for matching were calculated using age, BMI, FEV_1, OSA/OHS, $PaCO_2$ at discharge, Home O_2, and admission date.

[b] Matched groups further adjusted for variables OSA/OHS and $PaCO_2$ at discharge (After matching with propensity scores the characteristics OSA/OHS and $PaCO_2$ at discharge still differed between groups, thus necessitating further adjusting).

Lastly, given the retrospective and comparative nature of this study there is a possibility for disequilibrium between the study groups not captured by the variables studied.

Patients who require the use of bilevel NPPV during a hospitalization for AECOPD with acute hypercapnic respiratory failure have a high risk for significant morbidity and mortality in the interim [5,22]. In a study by Chu and colleagues, patients who were treated with NPPV for AECOPD with acute hypercapnic respiratory failure had a 79.9% readmission rate and a 49.1% mortality rate at one year [5]. The results from our study are promising and demonstrate that home NPPV may reduce readmission rates and improve event-free survival following hospitalization. Future prospective randomized and controlled trials are needed to evaluate the use of home NPPV in patients immediately following an admission for AECOPD with acute hypercapnic respiratory failure to substantiate the results from our retrospective study.

In conclusion, our retrospective study has demonstrated that following an admission for AECOPD with acute hypercapnic respiratory failure patients who used bilevel NPPV post discharge at home on a daily basis had lower readmission rates, reduced readmissions requiring a stay in the intensive care unit, and improved event-free survival. Patients are at a high risk for hospital readmissions and mortality following an admission for AECOPD with hypercapnic respiratory failure, and continued home use of nocturnal NPPV after discharge may be a consideration for treatment in this population. Prospective, randomized and controlled studies are needed to corroborate our results reported from this retrospective analysis.

Conflict of interests/Acknowledgments

Author contributions: Dr. Galli contributed to study concept and design, data collection, analysis and interpretation of data, and drafting and revision of the manuscript. Dr. Krahnke contributed to study concept and design, analysis and interpretation of data, and revision of the manuscript. Dr. Criner served as the guarantor of the paper, contributed to study concept and design, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, and approval of the final manuscript.

Dr. Mamary and Dr. Shenoy contributed to study concept and design, and analysis and interpretation of the data. Dr. Zhao performed statistical analysis and interpretation of data.

Financial/nonfinancial disclosures: Dr. Criner has served on Advisory Committees for Dey, Boehringer Ingelheim, Ikaria, Uptake Medical, PortAero and Pulmonx, Inc. Dr. Criner has received research grants from: Boehringer Ingelheim, Forest, Actelion, GlaxoSmithKline, Advanta, Daiichi Asubio, Pfizer, Roche and Novartis Pharmaceuticals, Emphasys Medical, Inc., and Aeris Therapeutics. All research grant monies are deposited and controlled by Temple University. Dr. Galli, Dr. Krahnke, Dr. Mamary, Dr. Zhao, and Dr. Shenoy have no disclosures to report.

Role of sponsors: The content of this publication is solely the responsibility of the authors.

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